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Docket No. 10806-151

PATENT

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Andreas Castan	:	Paper No.:
Serial No.:	09/732,638	:	Group Art Unit: 1634
Filed:	December 8, 2000	:	Examiner: B. Sisson

For: **Production of Peptides**

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. 1.116

Box AF
Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Official Action dated July 25, 2002, Applicant request reconsideration of the patentability of claims 1-20 and 22-28, in view of the following remarks.

REMARKS

The Official Action dated July 25, 2002 has been carefully considered. Accordingly, the remarks presented herewith are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

Claims 1, 2, 4, 5, 9, 11, 22, 23 and 28 were rejected under 35 U.S.C. §102(a), (e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Nakamura et al, U.S. Patent No. 5,912,113. The Examiner asserted that Nakamura et al disclose a method of culturing a microorganism in a batch culture under aerobic environment whereby glucose

is added to the culture media in an oscillating manner. Specifically, the Examiner asserted that Nakamura et al teach that glucose may be added to the culture media at less than 2 minutes as well as less than or equal to 30 minutes; yeast as well as bacterial cultures may be used; and the oscillation speed is considered to have a wave amplitude that ranges from +/- 5% to +/- 60% of standard.

However, as will be set forth in detail below, Applicant submits that the methods defined by claims 1-20 and 22-28 are not anticipated by or, in the alternative, are nonobvious over and patentably distinguishable from Nakamura et al. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

More particularly, claim 1 recites a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. The oscillation amplitude has a wave period of from about 1 to about 30 minutes. The microorganism is a biological host selected from the group consisting of bacteria, yeast and animal cell. The cultivation conditions remain aerobic.

Applicant finds no teaching, suggestion or reference in Nakamura et al of methods for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium, wherein the cultivation is carried out "without exhaustion of the organic carbon source" during the oscillation period. In contrast, Nakamura et al teach a method for aerobically culturing a microorganism using fed-batch, continuous, or cell-recycling continuous cultures, wherein the feeding rate of the carbon source feed solution is determined by the "exhaustion of the carbon sources" in the culture medium contained in the cultivation vessel, as disclosed at column 4, lines 19-22 and 36-40. Nakamura et al, in fact,

teach away from the present invention defined by claim 1. As further described in the specification application at page 5, lines 8-10 "the carbon source should never be exhausted during the process and there is no need to for measuring its concentration during cultivation." Thus, Applicant finds no teaching, suggestion or reference by Nakamura et al of the presently claimed methods since the methods of Nakamura et al require "exhaustion of the carbon source" to determine the feeding rate.

Anticipation under 35 U.S.C. §102 requires the disclosure in a single prior art reference each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q. 2d 1337, 1341 (Fed. Cir. 1986). In view of the failure of Nakamura et al to disclose a method as defined by claim 1, particularly wherein the cultivation is carried out with oscillation and "without exhaustion of organic carbon source" during the oscillation period, the reference does not disclose each element of the claims under consideration and therefore does not support a rejection of the claims under 35 U.S.C. §102.

Moreover, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). In view of the failure of Nakamura et al to teach, suggest or recognize a method as defined by claim 1, particularly wherein the cultivation is carried out with oscillation and "without exhaustion of the organic carbon source" during the oscillation period, the reference does not provide an enabling disclosure of the present invention, and therefore does not support a rejection of the claims under 35 U.S.C. §103. It is therefore submitted that the rejections under 35 U.S.C. §§102 and 103 have been overcome. Reconsideration is respectfully requested.

Claims 1-5, 8-12, 22, 23 and 28 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al in view of Gschaedler et al, *Biotechnology and Bioengineering*, Vol. 63, No. 6, (June 1999). The Examiner asserted that Gschaedler et al

teach culturing E. coli where a recombinant peptide was produced. Thus, the Examiner asserted that it would have been obvious to use the bacterial culture, i.e., E. coli, of Gschaedler et al in the Nakamura et al method of culturing a microorganism.

Claims 6, 7, 13-20, 26 and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al and Gschaedler et al, as applied to claims 1-5, 8-12, 22, 23, and 28 above, and further in view of Honjo et al, U.S. Patent No. 5,824,502. The Examiner relied on Honjo et al as disclosing at length the recombinant production of human growth hormone (rhGH). The Examiner asserted that it would have been obvious to have modified the method of Nakamura et al with the recombinant production of human growth hormone, as disclosed by Honjo et al, in E. coli, as disclosed by Gschaedler et al.

Finally, claims 24-25 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al and Gschaedler et al, as applied to claims 1-5, 8-12, 22, 23, and 28 above, and further in view of Bhattacharya et al, *Enzyme and Microbial Technology*, 20:355-360 (1977) and Takahashi et al, U.S. Patent No. 5,399,771. The Examiner asserted that Bhattacharya et al disclose the significance on maintaining certain levels of dissolved oxygen and that oxygen levels played a critical role in increased recombinant peptide production of E. coli. The Examiner further asserted that Takahashi et al disclose the need to vary the speed at which a culture is stirred such that the dissolved oxygen level stays at the appropriate level, and varying the stirring speed +/- 20% of standard is considered to be the result of routine experimentation. Therefore, the Examiner asserted that it would have been obvious to have modified the method of Nakamura et al and Gschaedler et al with the aspect of varying the stirring speed as disclosed by Bhattacharya et al and Takahashi et al.

However, as will be set forth in detail below, Applicant submits that the methods defined by claims 1-5, 8-12, 22, 23 and 28 are nonobvious over Nakamura et al in view of Gschaedler et al. Further, Applicant submits that the methods defined by claims 6, 7, 13-20,

26 and 27 are nonobvious over Nakamura et al in view of Gschaedler et al, and further in view of Honjo et al. Finally, Applicant submits that the methods defined by claims 24-25 are nonobvious over Nakamura et al in view of Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

As noted above, claim 1 is directed to the production of recombinant peptides by fed-batch cultivation carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed. The cultivation defined by claim 1 is carried out "without exhaustion of the organic carbon source" during the oscillation period. In contrast, Nakamura et al, as discussed in detail above, teach a method for aerobically culturing a microorganism wherein the feeding rate of the carbon source feed solution is determined by the "exhaustion of the carbon sources" in the culture medium. Moreover, Applicant finds no teaching, suggestion or reference by Nakamura et al of a method for the production of recombinant peptide by fed-batch cultivation wherein the cultivation is carried out with oscillation and "without exhaustion of the organic carbon source" during the oscillation period.

The deficiencies of Nakamura et al are not resolved by Gschaedler et al, Honjo et al, Bhattacharya et al and/or Takahashi et al. Specifically, Gschaedler et al disclose the use of E. coli as a host for the production of recombinant proteins. However, Gschaedler et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out with oscillation and without exhaustion of the organic carbon source, as required by claim 1. Honjo et al disclose a method for secretory production of recombinant human growth hormone (rhGH). However, Honjo et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out with oscillation and "without

exhaustion of the organic carbon source" during the oscillation period as required by claim 1. Bhattacharya et al disclose the effects of dissolved oxygen and oxygen mass transfer on overexpression of target gene in recombinant E. coli. However, Bhattacharya et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out with oscillation and "without exhaustion of the organic carbon source" during the oscillation period as required by claim 1. Finally, Takahashi et al disclose the preparation of thiomarinol B by the oxidation of thiomarinol. However, Takahashi et al fail to teach, suggest, or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out with oscillation and "without exhaustion of the organic carbon source" during the oscillation period as required by claim 1.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, supra. In view of the failure of Nakamura et al in view of Gschaedler et al; Nakamura et al in view of Gschaedler et al, and further in view of Honjo et al; and Nakamura et al in view of Gschaedler et al, and further in view of Bhattacharya et al and Takahashi et al, to teach, suggest or recognize a method for the production of recombinant peptide by fed-batch cultivation, wherein the cultivation is carried out with oscillation and "without exhaustion of the organic carbon source" during the oscillation period, the references do not provide an enabling disclosure of the present invention and therefore do not support a rejection of the claims under 35 U.S.C. §103. It is therefore submitted that the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§102 and 103 and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

Clare M. Iery
Registration No. 51,833
DINSMORE & SHOHL LLP
1900 Chemed Center
255 East Fifth Street
Cincinnati, Ohio 45202
(513) 977-8192

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